REMARKS

Claims 14-17 are pending and are rejected under 35 U.S.C. § 103. Applicants address each basis for rejection as follows.

Rejection under 35 U.S.C. § 103

Claims 14-17 are rejected under § 103 as being unpatentable over Jacques et al. (J. Alloys Compds. 213/214:286-289, 1994; "Jacques") in view of Deal et al. (J. Med. Chem. 42:2988-2992, 1999; "Deal") and Larsen et al. (US 2001/0008625A1; "Larsen '625") and further in view of Ma et al. (US 2003/0086868A1; "Ma"). Applicants respectfully traverse this basis for rejection.

Jacques discloses Thorium (IV) complexes with two polyaza polycarboxylic macrocycles, DOTA and HEHA. The compounds are considered to be both kinetically and thermodynamically stable. Only the abstract is relied on by the Office, and it clearly indicates that Jacques relates to an investigation into the solution conformation of different isomers of the chelates. There is no mention of radioisotopes, and therefore Applicants submit that Jacques, as relied on by the Office, does not describe radioactive decay, the daughter products resulting therefrom, or any effect this might have on the stability of the chelates. As no specific isotope of Thorium is mentioned in the abstract, Applicants submit that the disclosure does not provide a clear and unambiguous disclosure of which isotope was used. In the absence of this teaching, it appears likely that the most abundant thorium isotope, Thorium-232, would have been used. Thorium-232 has a half-life of 14 billion years and, given the long half-life, radioactive decay of thorium is not a factor in the complexes of Jacques. Accordingly, Applicants submit that the abstract of Jacques provides no information on the abilities of the DOTA and HEHA macrocycles to effectively encapsulate Thorium-227 and its decay product Radium-223.

The Office acknowledges, in Item 7 of the Office Action, that Jacques does not disclose complexes of Thorium-227 or complexes comprising a targeting moiety with

bioaffinity. However, based on other statements in the Office Action, it appears that the Office is taking the position that Jacques provides sufficient evidence that macrocycles of the type mentioned would be obvious choices for chelates capable of binding to Thorium-227 for administration to soft tissue. Applicants, for the reasons explained below, respectfully disagree.

Deal discloses complexes of Actinium-225 with similar ligands to those used in Jacques. The complexes are reported to possess increased stability and reduced toxicity over free Actinium-225 and complexes of this isotope with acyclic chelators. Applicants submit that Deal simply describes the well-known chelate effect, whereby complexes of bidentate or polydentate ligands are found to be more stable than those with unidentate ligands. Applicants submit that Deal provides to the skilled worker nothing more than confirmation of general knowledge that macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity. Deal, however, even if combined with Jacques, fails to provide the skilled worker with the necessary teachings which would render the pending claims obvious because Deal does not describe the suitability for such chelators in administering Thorium-227 in a soft-tissue targeting form. In fact, in the left hand column at page 2991, Deal states:

> [T]he extremely rapid elimination of ^{225}Ac-HEHA from the blood may not provide an opportunity for the isotope to dissociate within this time frame and these conditions, thereby presenting the appearance of an inert complex under *in vivo*.

In contrast, the complexes encompassed by the claimed invention are specifically designed to target soft tissue and remain at that site. Given that the complexes of Deal are eliminated extremely rapidly from the blood, it is readily apparent that these complexes are not useful for targeting soft tissue as is required by the pending claims.

Applicants submit that the complexes described by Deal provide a *carrier* for the radionuclide which is stable enough to allow it to be adequately distributed around the

body, but which then *releases* the isotope, enabling it to decay by α-emission and exert its cytotoxic effect. Deal aims to generate complexes which are stable enough to retain the radionuclide as it distributes itself around the body, but which can also eventually release the isotope. This contrasts with the complexes of the claimed invention, which are targeted and thus designed with the aim of retaining the isotope at the target site until radioactive decay. The success of the types of chelates disclosed in Deal therefore, if anything, teaches away from their suitability for use in the claimed invention. The distribution and release properties of the complexes described by Deal also indicate that such complexes would not be compatible with methods such as those described in Larsen '625 and therefore provides no motivation to combine the teachings of Jacques and Deal with those of Larsen '625.

The Office cites Deal primarily as evidence that multifunctional chelates which are not bone targeting and which do not possess phosphate groups are capable of forming stable complexes with the α-emitter Actinium-225. The Office then asserts that, because Jacques has demonstrated that such chelates can also form stable complexes with thorium (IV), it would be obvious to the skilled worker that the α-emitter Thorium-227 could also be complexed stably using these types of ligands. The Office further bolsters this assertion by pointing to Larsen '625 as disclosing that both Thorium-227 and Actinium-225 are known to be useful in the treatment of cancer and, because they are both α-emitters, it is reasonable to assume that ligands capable of forming stable complexes with one would also be capable of doing so with the other. Applicants respectfully disagree.

To be effective in a targeted method, a complex must not only successfully bind Thorium-227, but must also retain this binding for at least the order of the radioactive half-life if a reasonable proportion of the administered material is to have therapeutic benefit. The complexes of Deal, as is evident from the above citation, do not have these properties required for a targeting complex. As such, Deal not only does not describe complexes containing Thorium-227, the Actinium-225 complexes it does describe would

also not be useful for targeting a soft tissue. Applicants submit that Deal simply cannot support the contention that Thorium-227 could be used in a targeting complex as the reference entirely fails to describe a targeting complex.

Moreover, as is clearly indicated in the application as filed, prior to filing of the present application, the understanding in the art was that Thorium-227 is not suitable for use in the treatment of soft tissue disease because the minimum therapeutic dose of Thorium-227 would generate more than the lethal dose of its daughter, Radium-223. Given that, in a soft tissue targeting complex, no way was known to control the fate of the Radium-223 daughter nuclide and keep it safely retained, it would be free to distribute around the body with potentially fatal effects on the patient. The use of Thorium-227 was therefore not considered.

The present inventors surprisingly discovered that Thorium can be utilized successfully by way of the complexes currently claimed. None of the prior art cited by the Office suggests that the chelates encompassed by the claims would be useful for treating humans as complexes of this sort, which maintain control over Thorium-227 until it decays, had not been considered.

As an additional point, in response to the Office's suggested equivalence of Actinium-225 and Thorium-227, it should be noted that Actinium-225 decays to Francium-221, which produces three toxic alpha decays before reaching stable Bismuth-209, whereas Thorium-227 generates Radium-223, which generates four alpha emissions before reaching stable Lead-207. Thus, on first inspection, one would expect Radium-223 to be a third more toxic than Francium-221. The nature of Radium-223 as a calcium analogue would also be significant in expected bone marrow toxicity. The issues of toxicity of the daughter nuclide would therefore be far less significant when considering the use of Actinium-225 in radioimmunotherapy. This is reflected in Deal, in which the eventual release of the Actinium-225 from the chelate is desired. It is furthermore evident from this analysis that a skilled worker would not simply substitute Thorium-227

for Actinium-225 as the Office suggests on the basis of Larsen '625. Larsen '625 discloses that Astatine-211, Lead-212 (as a generator), Bismuth-212, Bismuth-213, Radium-223, Radium-224, Actinium-225, and Thorium-227 are all examples of alpha emitters. Beyond this, which has been known for decades, Larsen '625 makes no further comment on the similarity, or any other properties, of any members of this group. The Larsen '625 document therefore contributes nothing towards rendering obvious the complexes encompassed by the pending claims.

Further, Applicants note that the pending claims require the complex to contain Thorium-227 and a bifunctional chelator attached to a soft tissue targeting group and not having a phosphate bone-targeting moiety. None of the cited references, either individually or in combination, teach or suggest that suitable bifunctional chelators can be attached to soft tissue targeting moieties other than folate and maintain control of the radioisotope sufficiently to be of therapeutic value.

The Office cites Ma as evidence that the binding of a biological molecule to a radionuclide chelate was known at the time of filing the present application and that it would therefore be obvious to functionalize the complexes of Jacques or Deal with a moiety which would target the complex to soft tissue. Again, however, Applicants note that the complexes in Deal are designed to be *carriers* for the radionuclide Actinium-225. As indicated at paragraph [0006] of Ma, toxicity of Actinium-225 is a considerable issue with a number of known chelators. Paragraph [0005] of Ma points to this being the result of the cascade of alpha and beta emissions caused upon decay. Given that, as indicated above, Thorium-227 is known to generate one third more toxic alpha decays before reaching a stable daughter than Actinium-225, Applicants submit that the skilled worker reading Ma would be disinclined to attempt to substitute an apparently more toxic alternative (Thorium-227) for Actinium-225.

As Applicants pointed out in previous responses, without knowledge of the present invention, there would be no expectation that Thorium-227 could be complexed as

claimed for use in targeting soft tissue. In particular, the known toxicity of α-emitting daughter nuclei and the fact that the prior art only discloses the use of Thorium-227 in contexts where control of these daughters can be maintained by a means other than the chelate itself, i.e., localization to bone, would not motivate one skilled in the art to generate a soft tissue targeting complex of Thorium-227. None of the documents cited by the Office teach or suggest that bifunctional chelators in which the group bonded to Thorium-227 is not a phosphate group or bone targeting group would be capable of providing a complex in which the radionuclide could be stably retained and could provide a route to the successful application of Thorium-227 in targeting soft tissue without fatal or intolerable side-effects.

For the reasons set forth above, Applicants submit that the presently claimed invention is nonobvious over the combination of cited art. The present rejection under 35 U.S.C. § 103 should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Applicants also provide a Petition to extend the period for replying to the Office Action for three (3) months, to and including August 2, 2011.

Authorization is hereby provided to charge the extension fee required by 37 C.F.R. § 1.17(a), as well as any other fees or to apply any credits, to Deposit Account No. 03-2095.

Respectfully submitted,

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